IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF WEST VIRGINIA
AT CLARKSBURG

MERCK SHARP & DOHME CORP.,

Plaintiff,

v.

MYLAN PHARMACEUTICALS INC.,

Defendant.

Civil Action No. 19-cv-101 (IMK)

MERCK'S BRIEF IN RESPONSE TO
MYLAN'S OPENING POST-TRIAL BRIEF

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The evidence at trial overwhelmingly demonstrated the nonobviousness of Merck's 1:1 sitagliptin dihydrogenphosphate ("DHP") salt and the related method of treatment. The person of ordinary skill in the art ("POSA") would not have been aware of any problems with sitagliptin free base or the HCl salt, would not have had the necessary data to run a salt screen, and would not have had any reason to select phosphoric acid. In view of salt formation's unpredictability, the POSA would have had no idea whether 1:1 sitagliptin DHP could even form, much less that it would exhibit the desirable properties that turned it into a successful drug. And without biological data, the POSA would not have expected it to be therapeutically effective.

Rather than grapple with this one-sided trial record, Mylan contends that obviousness-type double patenting ("OTDP") does not require an inquiry into motivation or reasonable expectation of success. That argument contravenes explicit Federal Circuit precedent and evinces the deficient nature of Mylan's OTDP case. Mylan also argues that *Pfizer v. Apotex* is controlling, eliding the fact that there was particularized evidence in that case directing the POSA to the claimed salt. Mylan put forward no similar evidence here and did not dispute that phosphate salts were known to exhibit *disadvantages*. On claim 19, Mylan accuses Dr. David MacMillan of bias, while rebutting essentially none of his testimony. Mylan has not established either motivation or reasonable expectation of success by clear and convincing evidence.

Mylan's § 112 defenses fare no better. The '708 patent's specification would have enabled the POSA to make all known forms of 1:1 sitagliptin DHP without undue experimentation. The specification also contains verbatim support for the claims, which would have allowed the POSA to recognize any form of 1:1 sitagliptin DHP that the claims cover. Instead of disputing these facts—which easily establish enablement and written description—Mylan again resorts to incorrect legal arguments, contending that the inventors of the '708 patent

were required to enable and describe particular hydrates that did not (and do not) exist and are not recited in the claims. Mylan's position flouts decades-old precedent that there is no need to enable or describe after-arising embodiments. Its § 112 defenses should be rejected.

I. MYLAN'S OBVIOUSNESS-TYPE DOUBLE PATENTING DEFENSE FAILS

Mylan's OTDP case rehashes art and arguments considered by the Patent Office during prosecution and the IPR filed by Mylan. The '871 patent is listed on the face of the '708 patent, JTX-1.1, and WO '498 is discussed in the specification, *id.*, 1:49-57. The Patent Trial & Appeal Board, moreover, rejected Mylan's IPR obviousness challenge to claim 3 over WO '498 and Bastin,[1] finding "there were numerous reasons why a POSA would not have made all the choices that would [have] been needed to arrive at the claimed subject matter," and crediting Merck's expert's testimony that there were no known problems with sitagliptin HCl and that "phosphates were known to reduce solubility and stability." IPR FWD 56. The PTAB also found "forming such salts is highly unpredictable" and Mylan had not cited a "specific screening or optimization protocol . . . [that] would have led to a 1:1 sitagliptin DHP." *Id.* at 55, 58. Although made in the context of claim 3, these findings apply equally to claims 1 and 2.

Mylan's OTDP case is materially weaker than its IPR challenge. First, in its IPR, Mylan had to demonstrate obviousness only by a preponderance of the evidence, which it failed to do. IPR FWD 58. Here, Mylan must prove invalidity by clear and convincing evidence. Second, Mylan's IPR challenge relied on the *entirety* of WO '498, while Mylan's OTDP case is properly limited to the *reference claims* of the '871 patent. *Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 689 F.3d 1368, 1380 (Fed. Cir. 2012). This vulnerability explains Mylan's resort to a kitchen-

[1] The PTAB did not consider the obviousness of claims 1, 2, or 19 because Merck swore behind those claims. Dkt. No. 104-1 ("IPR FWD") 42-52. Merck has now sworn behind claim 3 as well. Dkt. No. 123 ("JSOF") ¶ 70.

sink approach, arguing that both the '871 patent's specification and WO '498 should be considered. Those arguments are factually and legally baseless and do not, in any event, support the obviousness of the asserted claims. *Infra* I.D.

As in its IPR Petition, *see* IPR2020-0040, Paper 1 at 49-51, 54-55 (P.T.A.B. Oct. 30, 2019), Mylan makes *Pfizer v. Apotex* the centerpiece of its brief, Dkt. No. 175 ("Br.") 4-8, giving short shrift to the trial that occurred. Mylan's attempt to secure factual findings based on *Pfizer*—rather than the trial record—evinces the deficiency of Mylan's evidence and ignores the *Pfizer* Court's admonition that its holding was based on "the *particularized facts of this case*." 480 F.3d 1348, 1367 (Fed. Cir. 2007). Mylan's inaccurate portrayal of *Pfizer* is addressed throughout this brief. Of particular note, though, is Mylan's omission of the fact that, in *Pfizer*, multiple prior art references disclosed the benefits of using the claimed anion,[2] which "narrow[ed] the genus" of possible anions to "a few," including the claimed anion, and "predicted the results" of using that anion. *Id.* at 1363, 1367. Mylan has presented no similar evidence here—to the contrary, it was undisputed at trial that phosphoric acid salts were known to exhibit *disadvantages*; that the scope of available acids would not have been narrowed even with knowledge of sitagliptin's pKa; and that the properties of 1:1 sitagliptin DHP were unknown and unpredictable. *Infra* I.A.4, I.F, I.G.

Courts have repeatedly declined to follow *Pfizer* when confronted with similar facts as presented here, and the Federal Circuit has uniformly affirmed those judgments. Exemplary is *Valeant v. Watson*, which distinguished *Pfizer* where there were no "teachings suggesting that switching from [HCl] to the [claimed] salt would result in a more stable" formulation. 2011 WL 6792653, at *12 (S.D. Fla. Nov. 8, 2011), *aff'd sub nom. Valeant Int'l Berm. v. Actavis, Inc.*, 534

[2] When an acid donates a proton, it becomes a negatively charged ion, or an "anion."

F. App'x 999 (Fed. Cir. 2013). Similar is *Pfizer v. Mylan*, which held that "unlike in *Pfizer*, there was nothing in the prior art to suggest to one skilled in the art that [the claimed anion] was one of a limited subset of salts to choose, or even that a salt form of [the compound] would be beneficial." 71 F Supp. 3d 458, 474 (D. Del. 2014), *aff'd*, 628 F. App'x 764 (Fed. Cir. 2016). *Sanofi-Synthelabo v. Apotex* also distinguished *Pfizer* where "there was no prior art teaching that the [claimed] salt was particularly likely to be a successful salt form of" the drug and "additional prior art . . . might actually have led the [POSA] away from" the claimed acid. 492 F. Supp. 2d 353, 391-92 (S.D.N.Y. 2007). The Federal Circuit affirmed, finding no clear error in the district court's holding that "the facts distinguish this case from those in *Pfizer*." 550 F.3d 1075, 1089 (Fed. Cir. 2008). Like the challengers in those cases,[3] Mylan has failed to cite any evidence suggesting that a phosphate salt of sitagliptin (if it could form) would have had beneficial properties; to the contrary, there were reasons to believe a phosphate salt could exhibit instability or other problems, leading away from it. *Infra* I.A.4.

A. The POSA would not have been motivated to pursue 1:1 sitagliptin DHP.

Mylan errs at the outset in stating the legal standard, contending that OTDP does not "require inquiry into a motivation to modify the prior art," Br. 3 n.1, and that it "does not need to prove a POSA would *select* the DHP salt of sitagliptin," Br. 1. Federal Circuit cases are clear,

[3] Mylan tries to distinguish *Valeant* by arguing that the prior art taught the HCl salt and did not include a claim to pharmaceutically acceptable salts generally. *See* Br. 5 n.4. That is incorrect—*Valeant* explained that the prior art (U.S. Patent No. 3,819,706) "mentions a number of bupropion salts." 2011 WL 6792653, at *1. Claim 1 of that '706 patent covers bupropion "or an acid addition salt thereof." Ex. A. In any event, Mylan's argument is backwards—the challenger's case in *Valeant* was stronger than Mylan's since (unlike here) the prior art disclosed disadvantages of the marketed HCl salt. 2011 WL 6792653, at *1. Mylan also argues that *Pfizer v. Mylan* is inapposite because that case included a "lead compound analysis." Br. at 5 n.4. But the cited portion of the opinion is cabined to whether "the malate salt modification" would have been obvious, and the Court concluded that it would not have been. 71 F. Supp. 3d at 474.

however, that OTDP requires an analysis of motivation and expectation of success. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1298 (Fed. Cir. 2012) ("an analysis of [OTDP]—like an analysis under § 103—entails determining, *inter alia*, whether [the POSA] would have had reason or motivation to modify the earlier claimed compound to make the compound of the asserted claim with a reasonable expectation of success"); *see UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1327 (Fed. Cir. 2018) (same); *Eli Lilly*, 689 F.3d at 1378 (same). Mylan cites *Geneva* in arguing that OTDP does not require an inquiry into motivation, Br. 3 n.1, but *Otsuka* explicitly rejected that interpretation, explaining that "*Geneva* . . . involved nonstatutory double patenting based on anticipation, not obviousness." 678 F.3d at 1297-98. It is also black-letter law that obviousness requires a motivation to *select* the claimed invention. *Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1307 (Fed. Cir. 2015); *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1072 (Fed. Cir. 2012); *Knauf Insulation, Inc. v. Rockwool Int'l A/S*, 788 F. App'x 728, 733 (Fed. Cir. 2019) ("there must be some reason to select a species from the genus").

To prevail on OTDP for claims 1-2, Mylan must prove that the POSA would have been motivated to select the claimed species (1:1 sitagliptin DHP) from the reference genus (sitagliptin free base or a pharmaceutically acceptable salt thereof). That genus is large—there were over 100 pharmaceutically acceptable acids by the priority date, which could potentially form many more sitagliptin salts of different stoichiometries, Tr. 876:24-877:12, 878:21-879:3 (Myerson); *infra* I.B, I.C—and Mylan has not attempted to argue that any prior art would have guided the POSA to select 1:1 sitagliptin DHP in particular. Rather, Mylan's theory hinges on a hypothetical "salt screen."[4] Br. 7. Its theory is legally impermissible here, as it requires the

[4] Mylan's position that the POSA would have resorted to a salt screen, with many acids under undefined conditions, renders this an "obvious-to-try" case. *Infra* I.C. Mylan's brief avoids that phrase, likely because Mylan did not offer the requisite evidence to support such a theory.

POSA to conduct research based on non-prior art problems and information. *Infra* I.A.3. Moreover, to prevail on that theory, Mylan had to prove that the POSA would have (1) pursued a sitagliptin salt, rather than the free base; (2) pursued a salt other than sitagliptin HCl; (3) conducted a salt screen of sitagliptin; and (4) included phosphoric acid in that salt screen, all with a reasonable expectation of success. Mylan has not come close to making such a showing.

1. The POSA would not have abandoned sitagliptin free base.

Mylan has failed to establish that the POSA would have been motivated to move beyond sitagliptin free base, the only compound recited in claim 17 of the '871 patent. Bighley teaches that the "*first decision* to be made concerns the viability of the neutral compound." DTX-7_30 (emphasis added); Tr. 374:7-18 (Buckton), 847:13-20 (Myerson); *see* DTX-7_31; Tr. 846:22-847:9 (Myerson) (first step is "Determine need for salt form"). As of the priority date, many primary amine drugs like sitagliptin were marketed in the form of a free base, Tr. 373:21-374:6 (Buckton), 825:2-4, 845:23-846:18 (Myerson); PTX-274. Because it was undisputed that there were no disclosed problems with sitagliptin free base, Tr. 824:11-825:1 (Myerson), 375:19-376:7 (Buckton), the POSA would have had no reason to search for alternative salt forms. Tr. 825:5-8, 845:10-22, 846:22-847:20, 859:2-9 (Myerson); *Forest Labs. v. Sigmapharm Labs.*, 918 F.3d 928, 935-36 (Fed. Cir. 2019) (no clear error in "consideration of the unknown nature of the problem solved by the inventors"); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (claims nonobvious where POSA "would not have recognized the problem").

Mylan's argument that the POSA would have undertaken a salt screen, Br. 7, is incompatible with Bighley's teaching that, for "a high-melting water-soluble solid" free acid or base, "there is generally *no need to prepare a salt form*." DTX-7_32, 34 (emphasis added); Tr. 847:21-848:24 (Myerson). Bighley warns against preparing a "'laundry' list of salt forms" unnecessarily. DTX-7_30. As Dr. Myerson explained, the POSA would not "spend all the time

and effort on a salt screen if the free base is developable." Tr. 847:5-9; PTX-71.1; Tr. 98:6-99:6, 106:20-107:7 (Hansen) (Merck evaluated free base extensively before making salt priority).

Mylan cites *Pfizer* to argue that the POSA would have developed a salt to "improve . . . bioavailability." Br. 5, 7. In *Pfizer*, however, the parties disputed *which* salt to select, not *whether* to make a salt. 480 F.3d at 1361-62. Here, the prior art did not disclose any information about sitagliptin free base's bioavailability, much less a problem that needed solving. If the POSA had performed experiments, she would have learned that the free base *already* had good solubility, Tr. 849:2-18 (Myerson), 103:10-104:4 (Hansen), 376:13-18 (Buckton), which is how salts enhance bioavailability, Tr. 287:13-17 (Buckton). And the experts agreed that the free base was a high-melting solid. Tr. 849:19-850:20 (Myerson), 1006:10-14 (Buckton). The POSA following Bighley thus would have had no reason to prepare salts of sitagliptin, even if the POSA had access to non-prior art testing of that compound.[5] Tr. 850:21-851:2 (Myerson).

2. The POSA would not have abandoned sitagliptin HCl.

If sitagliptin free base proved unacceptable, the POSA's next step would have been to evaluate sitagliptin hydrochloride (HCl), which is, by far, the most common acidic counterion, used in almost half of approved salts. Tr. 825:11-16, 859:15-22, 874:11-14 (Myerson), 295:19-296:2, 377:20-25 (Buckton); DTX-7_4-5; DTX-12_4. The Gould reference directed the POSA to "immediately progress to the hydrochloride salt and evaluate other forms *only if problems with the hydrochloride emerge*." DTX-12_5 (emphasis added); *see* DTX-7_31 (decision tree says "[p]repare [the] hydrochloride salt" before investigating other salts). It was undisputed that there were no problems with sitagliptin HCl disclosed in any prior art or the '871 patent. Tr. 825:17-

[5] The free base was unsuitable because of (non-public) stability issues, Tr. 104:15-107:17 (Hansen); PTX-71.7, but Mylan has not argued that instability would have motivated the POSA.

826:5 (Myerson), 380:8-381:17 (Buckton); IPR FWD 56. As such, the POSA would have tested sitagliptin HCl first and would have investigated other salts only if the HCl salt presented problems. Tr. 826:6-9, 860:2-862:15, 869:15-870:9 (Myerson). Merck synthesized sitagliptin HCl before screening for other salts. Tr. 107:20-108:14 (Hansen); PTX-71.7.

Mylan only engages with the HCl salt issue in a footnote devoid of any explanation other than bare citations to *Pfizer* and Dr. Buckton's testimony. Br. 8 n.6. *Pfizer*, however, does not address this issue, and neither Gould nor Bighley are cited. Moreover, unlike here, there was particularized evidence in *Pfizer* directing the POSA to the claimed salt. *Supra* pp. 3-4; 480 F.3d at 1363. Dr. Buckton testified that Bighley's decision tree meant that many acids should be tested simultaneously. Tr. 301:2-20. This is contrary to the explicit teaching of the references and violates the admonition to avoid unnecessary, wasteful salt screening. DTX-7_30. Dr. Buckton, moreover, conceded that Bighley's tree is written "in a sequential manner" and that HCl would have been a "logical first choice for . . . a salt form." Tr. 326:5-9, 376:24-377:8.

Finally, although Merck opted not to pursue sitagliptin HCl, Tr. 128:10-24 (Hansen), Dr. Buckton conceded that sitagliptin HCl *is* suitable for development, Tr. 1006:16-25 (Buckton), 870:10-15 (Myerson). Mylan has not established that—if the POSA had investigated sitagliptin HCl—she would have failed and undertaken a salt screen.

3. The POSA would not have conducted a salt screen.

The POSA would not have been motivated to screen for potential salts of sitagliptin for another reason: the absence of evidence of that compound's excellent biological activity. Tr. 827:24-828:10, 872:25-873:7 (Myerson). No reference disclosed such data. To the extent it can be considered,[6] the '871 patent's specification only discloses weak *in vitro* potency that is not

[6] Mylan does not argue that the biological data in the '871 patent may be considered for OTDP.

specific to sitagliptin. *Infra* I.F. The POSA would thus not have been motivated to develop that compound. Tr. 873:11-16 (Myerson), 770:1-4, 774:7-18 (MacMillan).

The POSA also would not have had access to the information necessary to conduct a salt screen of sitagliptin, such as its pKa and solubility.[7] Tr. 829:6-830:12, 870:25-871:6, 873:17-874:6 (Myerson), 282:12-283:14, 284:13-285:25, 382:3-382:24 (Buckton). Neither the prior art nor the '871 patent disclosed that information.[8] Tr. 382:15-17, 383:6-10, 384:23-385:24 (Buckton), 829:6-830:12, 871:4-6, 872:11-21 (Myerson).

Disputing none of these facts, Mylan contends that the POSA would have measured sitagliptin's pKa.[9] Br. 8 n.7. In addition to ignoring the other data needed to initiate a salt screen, this argument is legally impermissible. Mylan "cannot establish obviousness through non-prior art experiments." *In re Armodafinil Patent Litig. Inc.*, 939 F. Supp. 2d 456, 502 (D. Del. 2013); *see Bristol-Myers Squibb Co. v. Teva Pharms. USA*, 752 F.3d 967, 974 (Fed. Cir. 2014) (rejecting reliance on unknown toxicity data because obviousness evaluated from "perspective of a [POSA] *at the time of invention*" (citation omitted)).

4. The POSA would not have selected phosphoric acid.

Even if Mylan could demonstrate that the POSA would have conducted a salt screen, that does not get Mylan to 1:1 sitagliptin DHP. By the priority date, there were over 100 acids the POSA could have selected from. Tr. 876:24-877:12 (Myerson); DTX-7_4-5 (100+ acids); DTX-

[7] Dr. Buckton also testified that the POSA would have needed to measure stability, which was not disclosed in the art. Tr. 382:3-11, 385:9-13. The POSA also would have wanted information about dose and dosage form, which was likewise not disclosed. Tr. 830:13-832:11 (Myerson).

[8] Mylan observes, without explanation, that pKa and other properties are not in the '871 patent's definition of "pharmaceutically acceptable salts." Br. 4 n.3. That is irrelevant, as it was not disputed that the POSA would have needed that information *before* conducting a salt screen.

[9] Mylan correctly abandons its argument that the POSA could have estimated pKa, in view of the unreliability of such estimates and the inconsistent testimony from its IPR expert. Tr. 871:7-872:10, 872:22-24 (Myerson), 735:12-14 (Wenslow), 383:20-385:8 (Buckton).

21_213-14 (69 acids); *see* Tr. 737:10-21 (Wenslow), 366:22-367:11, 388:8-12 (Buckton). The POSA would have screened no more than about ten acids. Tr. 877:19-878:8 (Myerson), 293:14-19 (Buckton). The POSA would have had no reason to believe that phosphoric acid would have yielded a sitagliptin salt at all, much less a salt with favorable properties, Tr. 883:17-884:9, 902:2-5 (Myerson), 107:8-17 (Hansen); *infra* I.B, I.F, and Mylan offers no evidence that the POSA would have been motivated to select that particular acid to improve sitagliptin's properties. That omission alone distinguishes this case from *Pfizer*, where many references—including art specific to the claimed class of compounds—"narrow[ed] the genus" by suggesting the claimed salt would improve the drug's properties. 480 F.3d at 1363, 1366. Absent such evidence, courts have consistently rejected obviousness challenges to salt patents. *Supra* pp. 3-4.

Because the art provided no guidance as to which acid (if any) would improve sitagliptin's properties, the POSA intending to run a salt screen would have considered all nontoxic acids that had been used in approved products. Tr. 832:14-23 (Myerson). The POSA would have initially selected acids with a pKa at least two units below sitagliptin's. Tr. 838:21-839:10 (Myerson); *see* Tr. 283:11-14 (Buckton); Br. 7 (2-unit pKa difference suitable). No prior art disclosed sitagliptin's pKa to allow that selection; however, even if the POSA had access to the pKa of 7.7 that Mylan asserts, Br. 8, that would not have substantially narrowed the scope of candidate acids. Of the 69 acids recited in the *Handbook of Pharmaceutical Salts* ("*Handbook*"), 67 had a pKa below 5.7.[10] DTX-21_215-16; Tr. 877:11-18, 878:9-20 (Myerson), 403:12-404:3 (Buckton). Many pharmaceutical compounds containing a primary amine (like sitagliptin) were sold as salts other than phosphate, and both DPP-IV inhibitors in clinical trials used non-

[10] Using a pKa difference of 3, Br. 7, would not materially change the analysis, as 55 of the 69 acids in the *Handbook* have at least one pKa less than 4.7. DTX-21_215-16.

phosphate salts. Tr. 880:4-18 (Myerson), 404:4-407:15 (Buckton); PTX-37.3; PTX-722.2. The POSA would have had no reason to select phosphoric acid. Tr. 876:17-23 (Myerson).

Mylan argues that the POSA would have included phosphoric acid due to its frequency of use in marketed pharmaceutical products, Br. 7, but cites no evidence supporting this "popularity contest" theory of salt screening.[11] Indeed, this same argument was rejected in *Valeant* (in which Dr. Buckton also testified), because the purported popularity of an acid "is simply not probative" as to whether that acid would improve the properties of a compound. 2011 WL 6792653, at *11; *see also Pfizer*, 480 F.3d at 1363 (frequency of use "not highly probative").

On the facts, Mylan's argument also falters. Other than HCl at ~50%, no acids were commonly used. Tr. 874:15-19 (Myerson). Phosphoric acid was used in less than 3% of salts, Tr. 875:11-14 (Myerson); DTX-7_4, and Mylan cites no evidence that (apart from HCl) minor differences in frequencies would have motivated the POSA. This is especially true for phosphoric acid, whose prevalence was *decreasing* at the priority date. Tr. 874:20-875:23 (Myerson); DTX-6_2; DTX-7_4. In the period from 1995–2006—encompassing the 2002 priority date, JSOF ¶ 69—only 2 new phosphate salts were approved (out of 101 basic drugs), 1 of which was sitagliptin phosphate. PTX-111.11; Tr. 397:7-399:8, 402:7-403:7 (Buckton), 875:24-876:10 (Myerson); PTX-723.2. The trend leading up to the priority date was to use stronger acids like HCl and new acids. PTX-111.11; Tr. 389:17-19, 400:11-401:6 (Buckton) ("people are having to add more salts[] which are strongly acidic"); DTX-7_3 ("increase of approximately 40% in the types of anionic salts"). These trends led *away* from phosphoric acid.

There was good reason for the POSA to avoid phosphoric acid. Phosphate salts have "a

[11] Mylan's citation of Bastin on this point, Br. 7, is particularly inapt, given that *none* of the examples in Bastin included a phosphoric acid salt. *Infra* I.B.

tendency to form hydrates." DTX-21_137; Tr. 882:7-21 (Myerson), 355:12-356:5 (Buckton). Hydrates exhibit disadvantages, including dehydration during processing and lower solubility. Tr. 882:22-883:13 (Myerson); DTX-21_45; DTX-43_5-6 (hydrates can "dehydrat[e]" and "become chemically labile"); DTX-5_9; IPR FWD 62-63 ("widely-reported problems with hydrates"; "POSA would have sought to avoid hydrates"). There were many reports of phosphate salts with inferior properties, including solubility and stability, compared to other salts. Tr. 880:24-882:3 (Myerson); PTX-153.1 (phosphate less soluble than other salts); PTX-154.2 (same); PTX-185.3 ("Salts made from weak acids such as carboxylic or phosphoric acids are unstable and easily revert back to the free acid or base."); PTX-155.3-4 (phosphate salt less stable than others); PTX-219.1 (same); IPR FWD 56 ("phosphates were known to reduce solubility and stability versus hydrochloride salts"). These disadvantages—undisputed by Mylan—taught the POSA away from using phosphoric acid.[12] This is the opposite of *Pfizer*, where the prior art taught toward, not away from, the claimed salt. 480 F.3d at 1363.

Mylan cites the inclusion of "mineral acid salts" (of which phosphoric acid is one) in Bighley's decision tree. Br. 8. However, the *first two steps* of that tree are to evaluate the free base and HCl salt. *Supra* I.A.1-I.A.2. If the POSA followed the tree sequentially, as written, she would have had no reason to move beyond those steps, since no data suggested problems with sitagliptin free base or HCl. *Id.* On the other hand, if the POSA would have "do[ne] them all simultaneously," Tr. 298:16-17, 326:8-14, 379:25-380:5 (Buckton), as Mylan's expert testified, then the decision tree does not narrow the scope of acids, since it also includes "organic salts," DTX-7_31, which increases the number of acids dramatically. Together with "mineral acid

[12] Mylan may raise potential problems with HCl salts, but phosphate salts can exhibit the same issues and the art taught to use *organic* acids (not phosphate) if such issues arose. Tr. 864:18-865:23, 867:15-868:6 (Myerson); DTX-235_18; DTX-7_17; *Valeant*, 2011 WL 6792653, at *9.

salts," which are derived from inorganic compounds, Tr. 865:18-19 (Myerson), the complete Bighley tree effectively encompasses salts of all possible acids. Tr. 371:5-8 (Buckton).

B. The POSA would not have had a reasonable expectation of success of obtaining 1:1 sitagliptin DHP.

Mylan also has not proven a reasonable expectation of obtaining 1:1 sitagliptin DHP. Rather, the evidence is overwhelming that salt formation is unpredictable, Tr. 837:22-25, 838:1-17, 840:4-841:3, 883:17-884:9 (Myerson); PTX-111.2; DTX-21_62 ("[n]o predictive procedure" to determine whether salt forms "reported in the literature"), a fact cited in prior decisions. IPR FWD 34 ("making salts like those disclosed in the '708 patent and prior art is an unpredictable endeavor"); *id.* at 51 n.32, 58 ("forming such salts is highly unpredictable"); *Valeant*, 2011 WL 6792653, at *7 ("As a general rule, salt selection is an unpredictable art."); *Pfizer*, 71 F. Supp. 3d at 474 (noting "inherent unpredictability of acid salts").[13] Even Mylan's IPR expert—whom it replaced for this trial—agreed that salt formation at the priority date was "a trial and error process."[14] IPR FWD 22; *see* Tr. 883:17-884:9 (Myerson).

Here, the art provided no direction as to how to make *any* phosphoric acid salt of

[13] Mylan quotes from *Pfizer* about expectation of success, Br. 5-6, but *Pfizer* involved evidence not present here, including art indicating the claimed salt would form and have advantageous properties. 480 F.3d at 1363-66 (POSA "capable of further narrowing that list of 53 anions to a much smaller group, including benzene sulphonate, with a reasonable expectation of success"). There is no evidence here that prior art "predicted the results" of a 1:1 sitagliptin DHP salt. *Id.* at 1367; *see Pfizer*, 71 F. Supp. 3d at 474 (distinguishing *Pfizer v. Apotex* on similar grounds).

[14] Although Mylan's new expert, Dr. Buckton, testified that salt formation is predictable, he nonetheless agreed that the POSA could not predict when one would *not* form a salt. Tr. 410:14-20. His testimony was also inconsistent with the fact that he is an inventor on a patent claiming a 1:1 phosphate salt, where the prior art described "the compound and generically its pharmaceutically acceptable salts." Tr. 417:3-418:4 (Buckton); PTX-477.9, .24. Employing a salt screen, he "surprisingly found that [the compound] forms stable acid addition salts." PTX-477.9; Tr. 419:10-19 (Buckton). That contemporaneous account accords with the experience of Merck's witnesses. Tr. 739:14-20 (Wenslow) ("We never expected any salt to come out of solution. That was always a surprise."), 884:14-25 (Myerson).

sitagliptin. Tr. 884:10-13 (Myerson). Many variables affect salt formation. IPR FWD 66; *e.g.*, Tr. 834:3-24, 889:8-16 (acid-base ratio), 890:7-17, 890:18-891:21 ("wide variety of solvents"), 891:22-892:9 (method of isolation) (Myerson); DTX-43_66-72; PTX-99.7-10; DTX-21_77-78; DTX-5_2. Considering these variables in combination, "the number of potential experiments is exceptionally large," Tr. 892:16-24 (Myerson), and the prior art provided no guidance as to which, if any, might yield 1:1 sitagliptin DHP. IPR FWD 22 (Mylan's IPR expert agreeing that "You wouldn't know without performing research whether a phosphate salt of sitagliptin would form without doing that work"). Mylan does not identify the parameters for a screen, much less cite evidence that those unspecified parameters would yield 1:1 sitagliptin DHP.

Moreover, the POSA would have recognized that phosphoric acid and sitagliptin could have potentially formed salts with a stoichiometry (*i.e.*, base-acid ratio) other than 1:1.[15] Phosphoric acid contains three protons that may be donated to form salts, Tr. 820:10-20 (Myerson); Br. 8, and sitagliptin can receive at least two protons to form salts, Tr. 821:11-13 (Myerson). The POSA would have understood that it was possible that sitagliptin and phosphoric acid might form, for example, 2:1, 3:2, and 1:2 salts. Tr. 820:7-822:3 (Myerson). And, in fact, those non-1:1 salts have now been synthesized, Tr. 821:21-822:3, 888:12-889:3 (Myerson); JSOF ¶¶ 119-20. However, the POSA could not have predicted which (if any) of those non-1:1 salts would form in advance.[16] Tr. 887:12-17, 892:25-893:2 (Myerson).[17]

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[15] Claim 17 of the '871 patent does not claim or disclose any information about the stoichiometry of potential sitagliptin salts. Tr. 366:2-4, 369:21-370:2 (Buckton), 845:4-9, 887:7-11 (Myerson).

[16] This is illustrated by the Koehler paper (unaddressed by Mylan at trial), in which the authors made 1:1 lidocaine salts of HCl and sulfuric acid, yet obtained a 1:2 salt with phosphoric acid, despite using an equimolar (1:1) ratio of lidocaine to phosphoric acid. Tr. 887:18-888:11 (Myerson), 412:24-413:10 (Buckton); PTX-154.2. That undercuts Mylan's unsupported assertion, Br. 8, that an equimolar ratio would have been expected to yield 1:1 sitagliptin DHP.

[17] Mylan wrongly contends that "all experts agreed that the 1:1 DHP salt would be expected to form." Br. 8. Dr. Myerson's testimony was precisely the opposite. Tr. 883:17-884:9 (Myerson).

Mylan's only response is that the POSA would have predicted salt formation and stoichiometry in view of the pKa of sitagliptin and phosphoric acid. Br. 7-8. But sitagliptin's pKa was not disclosed in any prior art. *Supra* I.A.3. Even were it properly considered, pKa differences relate to ionization of acids and basis *in solution*. Tr. 838:18-839:5, 884:14-25 (Myerson). Claims 1-2, covering the 1:1 sitagliptin DHP *salt*, require a *solid*. Tr. 819:18-25 (Myerson), 412:11-13 (Buckton) (agreeing that "salts are solid state form[s]"). Any pKa difference would not have predicted whether a solid would form.[18] Tr. 838:18-839:14, 884:14-25 (Myerson), 736:14-737:9, 738:25-740:2 (Wenslow) (Merck "would have no idea what may come out of solution," notwithstanding pKa values); DTX-21_63. The fact that Bastin performed three "comprehensive" salt screens—and, according to Mylan, tried phosphoric acid (even though there is no report of it), Tr. 411:20-22 (Buckton)—and no phosphate salt formed (despite pKa differences of greater than 2) demonstrates that Mylan is wrong. Tr. 885:1-16, 885:23-886:20 (Myerson), 410:24-411:4 (Buckton); DTX-5_4-6; DTX-21_182.

Mylan cites to work from a Merck inventor, Vicky Vydra, to argue predictability. Br. 9. This argument is foreclosed. 35 U.S.C. § 103(a) (pre-AIA) ("Patentability shall not be negatived by the manner in which the invention was made."); *Otsuka*, 678 F.3d at 1296 ("The inventor's own path itself never leads to a conclusion of obviousness."). In any event, Mylan's characterization is hindsight and overlooks the fact that just because the salt formed easily does

[18] Mylan argues that the pKa values of sitagliptin and the second proton of phosphoric acid are "too close" to form non-1:1 salts. Br. 8-9. But salts may form with a pKa difference of less than two. Tr. 839:15-840:3 (Myerson), 735:1-6 (Wenslow). They are not a "remote possibility," Br. 9, as Mylan stipulated that they *did* form. JSOF ¶¶ 119-20; Tr. 888:12-889:3 (Myerson); IPR FWD 33 ("non-1:1 phosphate salts of sitagliptin, such as 1:2, 2:1, and 3:2 salts, do exist and can be made by conventional techniques"), 41. Moreover, this argument relates *only* to salts with more base than acid; it was undisputed that sitagliptin may accept multiple protons and could form non-1:1 salts with more acid than base (as in Koehler). Tr. 821:11-13 (Myerson).

not mean it was predictable in advance. *See* IPR FWD 34 n.22 (argument that salt was allegedly "made easily" "does not mean that the reaction product was known or predictable"). Indeed, Ms. Vydra only obtained salts with five of eleven acids in her screen. Tr. 111:19-115:12 (Hansen); DTX-242_3. Of those five, salts failed to form in many solvents. DTX-242_3. Moreover, the HCl salt did *not* form, even though Merck synthesized it previously.[19] Tr. 114:15-115:4 (Hansen). And Dr. Hansen's experiments sometimes failed to produce the 1:1 sitagliptin DHP salt. Tr. 172:9-173:5 (Hansen). Considered as a whole, Merck's work confirms the unpredictability of salt formation.[20] Tr. 886:24-887:6 (Myerson).

C. 1:1 sitagliptin DHP would not have been obvious to try.

Mylan is not running a traditional obviousness argument. Unlike the patent challenger in *Pfizer*—who cited publications that "clearly directed the [POSA] to a pharmaceutically-acceptable acid addition salt made from benzene sulphonate" of the compound, 480 F.3d at 1366—Mylan does not point to prior art "clearly directing" the POSA to synthesize a phosphate salt of sitagliptin. Rather, Mylan's theory that the POSA would perform a salt screen and include phosphoric acid among many other acids is a thinly veiled "obvious to try" argument, which requires a "design or market need to solve a particular problem." *Grunenthal GmbH v. Alkem Labs. Ltd.*, 919 F.3d 1333, 1345 (Fed. Cir. 2019). Mylan failed to offer proof of such a need. No reference provided data for sitagliptin that would have motivated the POSA to develop that compound, and there were no known problems with sitagliptin free base or HCl that would

[19] The failure of the HCl salt to form, despite a pKa difference of more than 13 units from sitagliptin, *see* Br. 8, 14 (-6 v. 7.7), further undercuts Mylan's pKa-based arguments.

[20] Mylan argues that Dr. Hansen and Ms. Vydra testified that they "reasonably expected" 1:1 sitagliptin DHP. Br. 6. That is incorrect—the cited testimony concerns salt-formation experiments they performed and their analysis thereof. Both witnesses testified that those experiments were not predictable in advance. Tr. 110:7-15 (Hansen), 709:1-710:4 (Vydra).

have motivated the development of other salts. *Supra* I.A.1-3; Tr. 892:10-15 (Myerson).

To prevail on obvious to try, Mylan also must establish that there were "a finite number of identified, predictable solutions." *Grunenthal*, 919 F.3d at 1345 (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007)). The evidence demonstrated the opposite. There were over 100 pharmaceutically acceptable *acids*, which could potentially form a far greater number of *salts* with different stoichiometries. Tr. 876:24-877:12, 878:21-880:3 (Myerson). Mylan did not even try to quantify how many possible salts were in that genus. Numerous parameters could be varied in a screen to discover those salts, rendering the experimental space "exceptionally large." Tr. 892:16-893:23 (Myerson); *supra* I.B. It would not have been predictable which salts (if any) might form or what their stoichiometries would be. Tr. 883:17-884:9, 892:25-893:2 (Myerson); *supra* I.B. 1:1 sitagliptin DHP would not have been obvious to try.

D. Mylan wrongly relies on the '871 patent's specification and WO '498.

1. Neither reference is properly considered in the OTDP analysis.

In an attempt to overcome the deficiencies in its case, Mylan relies on a disclosure in the '871 patent's specification related to preferred acids. Br. 3-4. That disclosure is not properly considered. The "correct double patenting analysis . . . turns on an evaluation of what [the patentee] has claimed, not what it has disclosed." *Eli Lilly*, 689 F.3d at 1380. Consideration of the reference patent's specification is only proper "to the extent necessary to construe its claims" and to understand the claim's utility. *Id.* at 1379-80. Mylan argues that the list of preferred acids relates to the "meaning" of "pharmaceutically acceptable salt." Br. 3. That argument fails because, as Mylan's expert admitted, the POSA would have understood that term without the specification. Tr. 310:25-311:10 ("So you wouldn't need to look at this definition and you wouldn't need to look at the list of most preferred acids[.]"), 366:8-21, 368:1-14 (Buckton), 842:25-843:8 (Myerson); *Choon's Design, LLC v. Zenacon, LLC*, 2015 WL 539441, at *12 (E.D.

Mich. Feb. 9, 2015) ("no need to resort to the specification to determine . . . claim scope"). In any event—as Mylan admits, Br. 4—the '871 patent defines "pharmaceutically acceptable salt" as a salt "prepared from pharmaceutically acceptable nontoxic bases or acids." DTX-34, 6:38-41; Tr. 843:9-844:10 (Myerson). The experts agreed the list of preferred acids is *not* part of that definition. Tr. 368:15-369:9 (Buckton), 843:25-844:10 (Myerson).

Mylan also relies on WO '498, Br. 14 n.14, which the parties stipulated is "not available as prior art under 35 U.S.C. § 102(e) to the '708 patent to prove obviousness under 35 U.S.C. § 103, pursuant to 35 U.S.C. § 103(c)." JSOF ¶¶ 116-18. Mylan argues that—even though WO '498 is disqualified as an *obviousness* reference—it is an *obviousness-type double-patenting* reference. The purpose of § 103(c), however, was "to avoid the invalidation of patents under § 103 on the basis of the work of fellow employees engaged in team research." *OddzOn Prods., Inc. v. Just Toys, Inc.*, 122 F.3d 1396, 1403 (Fed. Cir. 1997). It is inconsistent with Congress's intent for a § 103(c)-disqualified reference to nevertheless be available for use in an OTDP analysis.[21] In assessing whether claims are patentably distinct for OTDP, courts engage in an inquiry that is "analogous to the obviousness inquiry under 35 U.S.C. § 103." *UCB*, 890 F.3d at 1323; *see AbbVie Inc. v. M. & T. Kennedy Inst.*, 764 F.3d 1366, 1378 (Fed. Cir. 2014) ("[T]he law of [OTDP] looks to the law of obviousness generally."). Following that authority, the PTO has held that "the disclosure of a commonly owned patent that meets the requirements of 35 U.S.C. § 103(c)" may not "be used as prior art in making an [OTDP] rejection." *Ex parte Hrkach*, 2011 WL 514313, at *5 (B.P.A.I. Feb, 9, 2011).[22] That accords with the purpose of

[21] Of course, the *claims* of a § 103(c) disqualified patent may serve as a reference for OTDP. But such a reference may not be used as prior art in *combination* with the reference claims.

[22] Mylan cites *Germeyer*, Br. 14 n.14, but that decision misapplies *In re Bartfeld*, 925 F.2d 1450 (Fed. Cir. 1991), which nowhere holds that § 103(c) is inapplicable to OTDP. Moreover, the

§ 103(c) and dictates that WO '498 is not prior art here.[23]

2. Neither reference renders 1:1 sitagliptin DHP obvious.

Even were it considered, WO '498 does not remedy Mylan's OTDP case.[24] First, WO '498 does not disclose any problems with sitagliptin free base and would not have motivated the POSA to abandon that compound. Tr. 375:19-21 (Buckton), 894:9-12 (Myerson); *supra* I.A.1. Second, WO '498 does not disclose any problems with sitagliptin HCl; to the contrary, Example 7 describes the synthesis of sitagliptin HCl, which would have encouraged the POSA to look at that salt, rather than run a salt screen. Tr. 381:1-13 (Buckton), 894:13-17 (Myerson); DTX-34, 32:1-42; *supra* I.A.2. Third, WO '498 does not disclose sitagliptin's pKa or solubility, which the POSA would have needed to run a salt screen. Tr. 382:15-17, 384:23-385:1 (Buckton), 829:12-14, 830:7-9 (Myerson); *supra* I.A.3. Fourth, the POSA would not have limited herself to the "particularly preferred" acids in WO '498. Those acids are not disclosed in conjunction with sitagliptin, and reference claim 17 is not limited to those acids. Tr. 894:20-895:10 (Myerson); DTX-34, 7:2-4, 41:1-14. The POSA would have recognized the list of preferred acids as boilerplate, given that only sitagliptin HCl was exemplified in WO '498. Tr. 895:11-20 (Myerson). WO '498 does not disclose the properties of 1:1 sitagliptin DHP or suggest that salt

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issue in *Germeyer* was only whether the *claims* were available for OTDP purposes, 2010 WL 1253701, at *5-6 (B.P.A.I. Mar. 29, 2010), which is not analogous to Mylan's attempt to use the entirety of WO '498.

[23] Were Mylan correct that § 103(c) is inapplicable for OTDP, it could have asserted the '871 patent *itself* as prior art in combination with the reference claims of the '871 patent. Mylan avoided this absurd position—which violates the prohibition on consideration of the specification—by selecting a different member of the '871 patent family for its obviousness "combination." That problem is not unique to this case—*every* patent disqualified under § 103(c) may be an OTDP reference. MPEP § 804. Mylan's interpretation would vitiate that statutory disqualification, since those patents could simply be used in their entirety for OTDP.

[24] For simplicity, § I.D.2 refers to WO '498, but the analysis is equally applicable to the identical disclosure of the '871 patent's specification. Tr. 896:21-897:4 (Myerson).

would be advantageous. Tr. 837:1-4 (Myerson); *supra* I.A.4. As the PTAB found, WO '498 would not have motivated the POSA to try to make a phosphate salt of sitagliptin. IPR FWD 56.

The POSA also would not have expected 1:1 sitagliptin DHP to form based on WO '498. Tr. 896:16-20 (Myerson). There is no salt-formation scheme using phosphoric acid in that reference, so Mylan argues that the POSA would have expected sitagliptin and phosphoric acid to form a 1:1 salt based on Example 7's use of HCl, since phosphoric acid is weaker than HCl. Br. 14. This stoichiometry argument ignores the uncertainty of whether *a salt would form at all*. *Supra* I.B. Example 7 is not an apt comparator in any event, including because phosphoric acid may donate three protons (to form non-1:1 salts) whereas HCl may only donate one. Tr. 820:4-13, 896:1-9 (Myerson); IPR FWD 28. Moreover, Mylan's argument based on acid strength is unsupported by any literature and is inconsistent with Koehler, which reported 1:1 salts with lidocaine and HCl/sulfuric acid and a 1:2 salt with the weaker phosphoric acid. *Supra* I.B & note 16; Tr. 896:10-15 (Myerson).

E. Claim 3 of the '708 patent would not have been obvious.

Claim 17 of the '871 patent is directed to the (R)-configuration of sitagliptin. Tr. 415:12-14 (Buckton). There is no information in claim 17 of the '871 patent (or any prior art) suggesting that the (S)-configuration would have been beneficial, Tr. 898:17-19 (Myerson), and the POSA would not have been motivated to modify the (R)-configuration of the reference claim to use the (S)-configuration. Tr. 898:13-16 (Myerson); IPR FWD 57-58 (claim 3 not obvious where there was "no expected or even theoretical benefit to making an (S)-enantiomer").

Unable to cite sitagliptin-specific evidence, Mylan relies on a general FDA statement about stereoisomers. Br. 10. Mylan's argument assumes the POSA would have submitted 1:1 sitagliptin DHP for regulatory approval. DTX-48_2 (discussing data that "should be included in the IND and NDA"). But the undisputed testimony from Dr. MacMillan was that the POSA

would not have been motivated to even *begin* development on sitagliptin. Tr. 774:7-18. Mylan's argument also ignores that claim 3 covers the 1:1 DHP *salt* in the (S)-configuration. Even were the POSA to assess the (S)-configuration for FDA purposes, the POSA would not have made the *salt* to do such testing. Tr. 898:20-25 (Myerson). Mylan offers no contrary evidence.

If considered, WO '498 would have taught away from claim 3 by stating a preference for the (R)-configuration. Tr. 415:8-11 (Buckton), 899:1-23 (Myerson); DTX-34, 4:1-13, 6:6-10. As the PTAB explained, WO '498's disclosure about stereoisomerism, Br. 15, is not specific to sitagliptin and would not have motivated the POSA to use the (S)-configuration. IPR FWD 58.

F. Claim 19 of the '708 patent would not have been obvious.

Even had the POSA tried to make 1:1 sitagliptin DHP (and she would not have), the POSA would not have had reason to *treat* patients with a therapeutically effective amount of it. The POSA would have selected a salt *before* administration to patients. Tr. 901:6-17 (Myerson); DTX-21_57 (final salt form picked "during the preclinical phase of development"); DTX-5_9. Selecting which salt to administer is based on the salts' properties, and the POSA would not have administered a salt with unsuitable properties. Tr. 835:20-837:14, 900:25-902:1 (Myerson). Because salt properties are unpredictable, Tr. 841:4-842:14 (Myerson), 995:5-8, 1012:9-12 (Buckton), 110:13-15 (Hansen), 740:3-6 (Wenslow); DTX-6_1; PTX-114.2; DTX-12_3; PTX-113.1-.2, and no prior art disclosed information about the properties of 1:1 sitagliptin DHP, Tr. 837:5-14 (Myerson), the POSA could not have predicted the properties of that salt, much less that it would have been *the* salt selected for clinical development. Tr. 902:2-9 (Myerson). This is a sufficient basis to find claim 19 nonobvious. Tr. 902:10-17 (Myerson).

The POSA also would not have had a motivation or an expectation of success of treating patients with a *therapeutically effective amount* of 1:1 sitagliptin DHP, as required by claim 19. As Dr. MacMillan explained, only 1 in 1000 compounds tested preclinically advance to human

clinical trials. Tr. 761:19-762:19 (MacMillan);[25] PTX-237. To enter clinical trials, a variety of *in vivo* safety, efficacy, and bioavailability data are required. Tr. 762:20-763:6 (MacMillan). To be administered to *patients*, a compound must prove safe in healthy volunteers. Tr. 763:8-764:17 (MacMillan). Those data are not disclosed in any prior art or the '871 patent, which does not contain *in vitro* data specific to sitagliptin, much less clinical or *in vivo* data. Tr. 771:16-773:7 (MacMillan). The POSA would not have had the requisite information to conduct Phase II trials on patients. Tr. 767:17-768:6, 769:14-25, 770:16-19, 777:17-778:13 (MacMillan). Indeed, administration of 1:1 sitagliptin DHP to patients based on the '871 patent's data would have been "reckless if not dangerous." Tr. 776:13-22, 790:16-791:8 (MacMillan).

Mylan also failed to establish a reasonable expectation of success in achieving a therapeutically effective amount of 1:1 sitagliptin DHP, which—in the '708 patent—is an amount of the compound that provides a desired biological outcome in a disease state when administered to a patient as determined by a clinician. Tr. 767:1-16 (MacMillan). The "vast majority of time," a compound exhibiting an *in vitro* effect will not prove effective in treating patients. Tr. 760:1-761:9, 765:2-766:12 (MacMillan); PTX-246.7. Regardless of any *in vitro* potency, the expectation of achieving a therapeutically effective amount of 1:1 sitagliptin DHP would have been "extremely low." Tr. 777:6-16 (MacMillan). If considered, the '871 patent discloses only that the exemplified compounds "had activity in inhibiting the [DPP-IV] enzyme . . ., generally with an IC_{50} of less than about 1 μM." DTX-34, 9:3-8. The POSA would have understood these non-specific, micromolar *in vitro* data to mean those compounds were only

[25] Mylan attacks Dr. MacMillan's credentials because he is not a clinician, Br. 13, but Dr. MacMillan has extensive medicinal chemistry experience, including identifying molecules to advance for further development. Tr. 753:13-754:13, 811:9-812:6 (MacMillan). Dr. Buckton, by contrast, is *not* a medicinal chemist (or a medical doctor). Tr. 269:16-270:7 (Buckton).

"weakly potent," particularly given the low nanomolar[26] potencies of successful DPP-IV inhibitors. Tr. 772:7-776:8 (MacMillan); PTX-249.17 ¶ 446; PTX-110.5-6; PTX-39.2. If anything, those data would have undermined any expectation of achieving therapeutic efficacy with 1:1 sitagliptin DHP. Tr. 776:23-777:5, 791:9-792:1 (MacMillan).[27] The POSA would have been surprised that 1:1 sitagliptin DHP was therapeutically effective, as Merck was. Tr. 790:3-15 (MacMillan), 147:17-148:10 (Hansen).

Neither Mylan nor its experts dispute the above testimony from Dr. MacMillan[28]—indeed, Dr. Buckton did not discuss motivation or expectation of success with respect to claim 19, Tr. 768:7-17 (MacMillan), which should be dispositive, *Otsuka*, 678 F.3d at 1298. Instead, Mylan cites repeatedly to *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 518 F.3d 1353 (Fed. Cir. 2008), but ignores its facts. The reference claim in *Pfizer* recited the compound and included a "therapeutically-effective amount" limitation that was stipulated to have the same meaning in the asserted and reference claims. *Id.* at 1363; *see Pfizer Inc. v. Teva Pharms. USA, Inc.*, 482 F. Supp. 2d 390, 476-77 (D.N.J. 2007). Here, by contrast, the reference claim does *not* recite a "therapeutically effective amount," or the compound at-issue (1:1 sitagliptin DHP),[29] and it is undisputed that "therapeutically effective amount" does *not* mean the same thing in the '871 and

[26] "Micromolar" is one thousand times less potent than "nanomolar." Tr. 774:1-6 (MacMillan).

[27] The salt form of 1:1 sitagliptin DHP—which can unpredictably affect therapeutic efficacy—further diminishes any expectation of success, as does the lack of a previously approved DPP-IV inhibitor. Tr. 757:21-758:2, 785:18-787:2 (MacMillan); PTX-113.1.

[28] Mylan's failure to rebut practically any of Dr. MacMillan's testimony makes its attacks on his credibility, Br. 13, particularly specious. If Dr. MacMillan truly were biased, where was the Mylan witness to offer contravening evidence? The reality is that Dr. MacMillan consults for ten different pharmaceutical companies. Tr. 754:2-13, 810:3-9 (MacMillan). Merck does not pay him a retainer or board fee, and there is no evidence that his consultations with Merck's medicinal chemists affected his testimony at trial. Tr. 810:21-23, 814:12-815:2 (MacMillan).

[29] Mylan's argument that the "active moiety" provides the therapeutic effect, Br. 12, ignores the undisputed evidence that the salt form can impact efficacy, Tr. 785:25-786:13 (MacMillan).

'708 patents. Tr. 767:1-16, 779:20-780:17 (MacMillan).

Rather, this case is closer to *OSI Pharmaceuticals v. Apotex*, in which the Federal Circuit found nonobvious methods of treating certain cancers using a therapeutically effective amount of a compound, in view of the lack of efficacy data and unpredictability of clinical trials. 939 F.3d 1375, 1384-85 (Fed. Cir. 2019). If anything, the *OSI* obviousness case—in which the prior art disclosed that the compound was a potent inhibitor that had completed Phase I trials, *id.* at 1380—was stronger than the present facts.

Mylan argues that "pharmaceutical composition" in claim 20 of the '871 patent would have motivated the POSA to administer sitagliptin to patients. Br. 11-12. Pharmaceutical compositions, however, have many uses beyond administration to patients—such as use in testing on animals—and the POSA would not have believed that sitagliptin (much less 1:1 sitagliptin DHP) could safely treat patients simply because claim 20 includes the words "pharmaceutical composition." Tr. 770:20-771:15 (MacMillan), 900:14-24 (Myerson).

Mylan cites the '871 patent's discussion of utility. Br. 11. However, the "utility" in that patent encompasses millions of compounds and relates to the earliest stages of Merck's DPP-IV research program. Tr. 783:23-785:23 (MacMillan). Those statements are based only on weak *in vitro* data, which would not have provided the POSA with a motivation or expectation of success.[30] Tr. 778:14-779:19 (MacMillan). Consistent with that broad scope of "utility" is the '871 patent's expanded definition of "therapeutically effective amount," which encompasses *in vitro* experiments by researchers. Tr. 779:20-780:17 (MacMillan); DTX-34, 8:9-13.

[30] Mylan argues, with no supporting expert testimony, that the claim structure of the '871 patent would have informed the POSA about sitagliptin's utility. Br. 11. This argument ignores Dr. MacMillan's testimony that the broad "utility" disclosed by the '871 patent would not have rendered obvious claim 19 of the '708 patent. Tr. 785:8-17. Mylan's attorney argument also improperly considers disclosures of the '871 patent outside the reference claim.

Mylan finally argues that the POSA could have determined an effective *dose*. Br. 12-13. This argument is beside the point, since the POSA would not have expected 1:1 sitagliptin DHP to be therapeutically effective *at any dose*. Tr. 767:1-16, 770:5-15, 791:9-792:1 (MacMillan). Moreover, the dose information Mylan cites—which is a "large range" that applies to millions of compounds—is aspirational and would not allow the POSA to arrive at an effective dose for 1:1 sitagliptin DHP.[31] Tr. 787:3-24 (MacMillan). The '708 patent, by contrast, discloses tablets containing a precise amount of 1:1 sitagliptin DHP, which the POSA would have understood to be therapeutically effective.[32] Tr. 788:4-789:11, 812:7-813:6 (MacMillan); JTX-1, 15:10-47.

G. 1:1 sitagliptin DHP exhibits unexpected properties.

The nonobviousness of claims 1, 2, and 19 is confirmed by 1:1 sitagliptin DHP's unexpectedly superior composite set of properties compared to the closest prior art—the HCl salt of Example 7 and sitagliptin free base. Tr. 903:3-10 (Myerson); *Eli Lilly*, 689 F.3d at 1382.

The experts agreed that a salt's composite properties were not predictable, and no prior art suggested that 1:1 sitagliptin DHP would have acceptable, much less outstanding, properties.[33] *Supra* I.F; *see* Tr. 835:20-837:14, 841:4-842:17 (Myerson), 995:1-997:5 (agreeing that "you can't predict in advance which salt would have the best composite set of properties"), 1012:9-12 (Buckton), 102:15-25, 107:8-17, 110:10-15, 125:1-4, 135:2-11 (Hansen), 750:2-6

[31] Mylan cites the phrase "therapeutically effective amount" in claim 23 of the '871 patent, Br. 12 n.12, but Mylan's expert offered no testimony about this claim. In any event, Mylan's argument improperly considers disclosures outside the reference claim and ignores the difference in the meanings of "therapeutically effective amount" between the '871 and '708 patents.

[32] Mylan argues that the '708 patent is "devoid of clinical data," Br. 13, ignoring the undisputed testimony that the POSA would have understood from the '708 patent that 1:1 sitagliptin DHP had been administered clinically in a therapeutically effective amount, Tr. 813:3-814:7 (MacMillan), which it had been, Tr. 147:12-149:17 (Hansen). Moreover, contrary to Mylan's repeated citations, Br. 12-13, the disclosures of the '708 patent are irrelevant to OTDP.

[33] Mylan argues that the goal is to improve a compound's properties, Br. 16, but that does not make predictable a salt's composite properties, Tr. 995:5-8, 1012:9-12 (Buckton).

(Wenslow). Nor is there any dispute that 1:1 sitagliptin DHP exhibits a suite of desirable properties, including superior particle morphology, low hygroscopicity, good chemical stability in solution, and high thermal stability. Tr. 101:1-102:14, 119:16-124:25, 128:17-24, 133:11-135:7 (Hansen), 748:7-750:1 (Wenslow), 903:14-909:6 (Myerson), 984:16-985:17 (Buckton); PTX-46.3-7, 45; PTX-82.1; PTX-41; PTX-42. By contrast, sitagliptin free base and HCl both exhibit poor particle morphology and stability. *Id.*; PTX-71; DTX-240_92-94. 1:1 sitagliptin DHP's properties were superior to other salts Merck assessed, *id.*; PTX-82.1 ("This is incredible. Not often do we see these."); Tr. 126:18-127:25 (Hansen), 1002:7-10 (Buckton), and "was the only salt obtained [] that demonstrated th[e] favorable combination of properties." *Sanofi-Synthelabo*, 492 F. Supp. 2d at 391, *aff'd*, 470 F.3d at 1379.

Dr. Buckton attempted to minimize the significance these properties, including solution stability and morphology. However, he admitted that "solution state stability can indicate the tendency for degradation" and can be relied on during development (as Merck did). Tr. 1002:11-22, 1004:2-19; PTX-71.7. He also conceded that morphology can affect processability, which is "one of the main goals of salt selection." Tr. 984:16-985:8, 995:14-996:20. In any event, Dr. Buckton acknowledged that the POSA would have considered the *composite* set of salt properties, Tr. 994:13-23, 1005:2-1006:5, and his critiques related to properties in isolation ignore the overall superior profile of 1:1 sitagliptin DHP.[34]

Mylan contends that Merck did not "tell the Court what one would expect from the DHP salt of sitagliptin." Br. 15. That is wrong—the POSA would have expected that a "compromise of properties for the salt form [would be] required." Tr. 909:24-910:23 (Myerson); DTX-12_3.

[34] Dr. Buckton's denigration of the properties of 1:1 sitagliptin DHP is particularly suspect given that those same properties are touted in his patent. PTX-477.17; Tr. 1005:2-1006:9 (Buckton).

No such compromise was needed for 1:1 sitagliptin DHP, which was "the same or superior in every significant property." Tr. 909:24-910:23 (Myerson), 127:13-25 (Hansen).

Mylan argues that the unexpected properties are not commensurate with the claims because Merck "abandoned anhydrous Form I-III," Br. 15-16, but unexpected results need only be "reasonably commensurate." *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011). In any event, the properties recited above *do* encompass anhydrous 1:1 sitagliptin DHP (*i.e.*, Forms I-III), among other forms. Tr. 133:11-134:2, 135:2-11 (Hansen), 902:22-909:23 (Myerson); PTX-46.3-7. Merck switched to the monohydrate because it exhibited *further* excellent properties, not because the anhydrous forms of the phosphate salt were poor. Tr. 975:2-7 (Myerson), 133:11-134:2 (Hansen). Dr. Buckton admitted as much, and *Mylan itself* is seeking approval for Form I. Tr. 1009:1-20, 1012:1-4 (Buckton); PTX-602.4.

Finally, Mylan argues that non-phosphate salts (approved for sale by third-parties outside the U.S. and described in Merck's WO '530 publication) indicate that 1:1 sitagliptin DHP's traits are differences in degree. Br. 16. But Dr. Buckton provided no testimony as to the properties of any salt approved abroad, much less that they exhibit a superior composite set of properties. With respect to WO '530, Dr. Buckton conceded that those salts—which are not prior art—were "not as good" as 1:1 sitagliptin DHP, and that he did not cite any hygroscopicity or chemical stability data. Tr. 987:22-23, 999:4-14, 1003:7-17. Mylan's citations of these other sitagliptin salts—devoid of any data—do not overcome the evidence that 1:1 sitagliptin DHP exhibited substantially, and unexpectedly, improved properties over sitagliptin HCl and the free base.

II. MYLAN'S ENABLEMENT DEFENSE FAILS

Mylan's argument depends on the incorrect premise that Merck needed to have enabled non-existent hydrates of 1:1 sitagliptin DHP—*e.g.*, di-, tri-, sesqui-, pentahydrates, and so on—rather than the only hydrate known to exist: the crystalline monohydrate. Br. 16-25. But the

evidence established that the '708 patent enables all known forms of 1:1 sitagliptin DHP, and Dr. Buckton could only speculate about some other hydrate arising in the future. Tr. 278:17-280:11 (Buckton), 918:24-920:19 (Myerson). Mylan cannot rely on a "possible" future state of the art—hydrate forms that may never exist—to invalidate the '708 patent. *See In re Hogan*, 559 F.2d 595, 606-07 (C.C.P.A. 1977); *Ex parte Cai*, 2011 WL 6127936, at *6 (B.P.A.I. Dec. 7, 2011).

Compounds and salts are routinely claimed at a general level, without reciting every "physical form," Br. 20, in which they could possibly exist. This ordinary practice does not mean that such claims are not enabled. The '708 patent undisputedly would have enabled the POSA to make 1:1 sitagliptin DHP "or a hydrate thereof," and every case to consider the enablement of compounds with different crystal forms has rejected Mylan's arguments.

A. The '708 patent enables the "full scope" of the claimed invention.

"Precedent establishes that '[t]he enablement requirement is met if the description enables any mode of making and using the invention.'" *Edwards Lifesciences AG v. CoreValve, Inc.*, 699 F.3d 1305, 1309 (Fed. Cir. 2012) (quoting *Johns Hopkins Univ. v. CellPro, Inc.,* 152 F.3d 1342, 1361 (Fed. Cir. 1998)). The claimed invention is 1:1 sitagliptin DHP "or a hydrate thereof." The experts agreed that "hydrate" refers to a structure containing 1:1 sitagliptin DHP and water in the crystal lattice. Tr. 353:20-354:4 (Buckton), 911:8-912:9 (Myerson). The '708 patent teaches *multiple* methods for achieving that structure. JTX-1, 6:29-7:42, 12:61-13:21; Tr. 357:11-358:5, 361:2-362:4 (Buckton), 137:13-144:1 (Hansen), 915:12-918:23 (Myerson).

The '708 patent not only enables "a hydrate," it enables the POSA to practice all known forms of 1:1 sitagliptin DHP without "undue experimentation." *Allergan*, 796 F.3d at 1309; Tr. 357:14-358:5, 361:2-362:4 (Buckton), 137:13-144:1 (Hansen), 915:12-918:23 (Myerson). It is undisputed that only seven forms of 1:1 sitagliptin DHP were known at the 2003 effective filing date of the '708 patent: four anhydrous forms (Forms I-IV), a solvate, the monohydrate, and the

dehydrated monohydrate (another anhydrous form). PTX-46.22, .33; JTX-1, 15:4-9; Tr. 129:2-132:17, 141:10-143:5, 147:4-9 (Hansen), Tr. 916:23–917:15, 920:24-921:12 (Myerson).[35]

Mylan argues only that the '708 patent does not enable Forms I-III, Br. 23-24, but no witness disputed Dr. Hansen's[36] and Dr. Myerson's testimony that the '708 patent teaches the POSA how to make these anhydrous forms by using (1) "a suitable C_1-C_5 alkanol" anhydrous solvent or (2) a water concentration below the "critical water activities" in the "General Methods," JTX-1, 6:29-7:42; Tr. 141:8-144:1, 146:1-25, 147:4-9 (Hansen), 916:4-918:23, 920:24-921:10, 924:8-11 (Myerson). Mylan conducted no testing to show otherwise.[37]

Mylan cites to Merck's application describing Forms I-III, Br. 24, but the existence of that later-filed application is irrelevant to enablement. *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1340 (Fed. Cir. 2003). If anything, the similarity between the methods in that application and the '708 patent's disclosures confirms that those disclosures enabled Forms I-III.[38] *Compare* DTX-2198.28 ¶ 116, *with* JTX-1, 6:56-67; Tr. 145:2-25 (Hansen). That the '708 patent teaches how to make all known forms of 1:1 sitagliptin DHP is dispositive.

The facts here are thus far stronger than *GlaxoSmithKline LLC v. Banner Pharmacaps, Inc.* ("*GSK I*"), in which claims to a compound and its "solvates"—a term Dr. Buckton conceded is broader than and includes "hydrate," Tr 353:20-355:11 (Buckton)—were enabled, despite the

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[35] Dr. Myerson also testified the POSA would be able to make an amorphous form. *Infra* II.C.

[36] Merck has compensated Dr. Hansen at his customary consulting rate for his time spent preparing for trial. This is routine for former employees who have to take time to testify in patent trials, and Mylan's criticism of this arrangement, Br. 24, is baseless.

[37] Mylan's observation that that the '708 patent does not identify Forms I-III, Br. 23, is irrelevant to enablement. *Ariad Pharms. v. Eli Lilly & Co.*, 598 F.3d 1336, 1352 (Fed. Cir. 2010).

[38] Without any supportive expert testimony, Mylan argues that Merck's prosecution statements are relevant to enablement. Br. 24. Those statements simply reflect that the Form I-III application expressly disclosed and claimed those forms, whereas the '708 patent does not. JTX-4.250; DTX-2198.30-32. Mylan's suggestion, Br. 24, that Dr. Myerson conceded anything on this issue—beyond the documents' contents—is simply not true. Tr. 969:20-970:19 (Myerson).

patent only describing a single "dissolved" solvate form. 2013 WL 4082232, at *9 (D. Del. Aug. 9, 2013), *aff'd*, 744 F.3d 725, 729-31 (Fed. Cir. 2014) ("*GSK II*"). Here, as in *GSK I*, "the [hydrate] of [1:1 sitagliptin DHP] is merely the compound in a different physical form," "[hydrates] of organic compounds have long been known in the art," "methods of creating and testing [hydrates] have also long been known," phosphate salts "are prone to [hydration]," and "the chemical compound of [1:1 sitagliptin DHP] is precisely claimed." *Id.* at *8-13; DTX-21_137; DTX-43_20-40, 61-97; DTX-5_4; Tr. 268:23-269:4, 355:22-356:5 (Buckton), 882:7-21, 911:8-913:1, 916:4-10, 926:6-928:2 (Myerson). *See also Ex parte Cai*, 2011 WL 6127936, at *5 (claim enabled despite lack of working example or guidance for "any specific hydrate or solvate form"); *Ex parte Germeyer*, 2010 WL 4961695, at *2-3 (B.P.A.I. Dec. 1, 2010) (same); *Ex parte Chern*, 2011 WL 5080233, at *2-3 (B.P.A.I. Oct. 24, 2011) (same); *Endo Pharms. Inc. v. Mylan Pharms. Inc.*, 2014 WL 334178, at *30-32 (D. Del. Jan. 28, 2014) (rejecting Mylan's argument that patent is invalid for failure to disclose and enable specific "salt-hydrate" of frovatriptan).[39]

B. Enablement is judged as of the filing date.

Faced with a mountain of evidence of enablement, Mylan focuses on a separate, irrelevant question: whether the '708 patent enables *unknown* hydrates, that did not exist at the priority date (or today), and that are not specifically claimed. Tr. 358:2-360:4 (Buckton), 922:2-7 (Myerson). But even if a new hydrate were to appear, that form would be irrelevant to the question of whether the '708 patent was enabled *as of its filing date*. *Hybritech Inc. v.*

[39] Numerous cases have upheld "hydrate" and solvate" claims without questioning enablement or description. *E.g.*, *Amgen, Inc. v. Sandoz Inc.*, 2021 WL 5366800, at *9 (D.N.J. Sept. 20, 2021); *Merck Sharp & Dohme Corp. v. Hospira Inc.*, 221 F. Supp. 3d 497, 502-03 (D. Del. 2016); *Alcon, Inc. v. Teva Pharms. USA, Inc.*, 664 F. Supp. 2d 443, 451 (D. Del. 2009); *OSI Pharms., Inc. v. Mylan Pharms. Inc.*, 858 F. Supp. 2d 341, 347 (D. Del. 2012). Dr. Buckton's own patent claims "salts" covering "any hydrate or solvate." Tr. 420:3-18 (Buckton); PTX-477.24.

Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). Evidence of a "later existing state of the art" does not prove lack of enablement. *Hogan*, 559 F.2d at 606; *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 555 F. App'x 961, 967 (Fed. Cir. 2014) ("Where a claim has been construed to cover a chemical compound, the specification is not deficient merely because it does not disclose how to prepare a particular form or mixture—among hundreds of possible permutations—of that compound."). The law simply "does not expect" the disclosure of "knowledge invented or developed after the filing date," as that is "impossible." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1254 (Fed. Cir. 2004).

For example, in *Hogan*, the claims were directed at a compound, which (at the time of filing) only existed as a *crystalline* form. 559 F.2d at 598, 605. An *amorphous* (non-crystalline) form was subsequently discovered, but the Federal Circuit's predecessor court held that the patentee was not required to enable that form, as it would "impose an impossible burden on inventors" and "the patent system." *Id.* at 606; *see also id.* ("To restrict appellants to the crystalline form disclosed, under such circumstances, would be a poor way to stimulate invention, and particularly to encourage its early disclosure."). The case for invalidity here is *worse* for Mylan because, to this day, no new hydrate of 1:1 sitagliptin DHP has been found.[40]

The cases that Mylan relies on, Br. 16-19, are distinguishable because they either involve claims reciting functional or aspirational results that the patent did not disclose structural or other

[40] "[U]nclaimed elements need not be enabled." *WesternGeco L.L.C. v. ION Geophysical Corp.*, 876 F. Supp. 2d 857, 867 (S.D. Tex. 2012); *Edwards*, 699 F.3d at 1310; 3 Ann. Pat. Dig. (Matthews) § 20:48. The asserted claims do not recite a limitation directed at any specific hydrate (*e.g.*, a dihydrate). Just because such a future hydrate may be patentable itself does not mean the original invention (a claim to 1:1 sitagliptin DHP "or a hydrate thereof") is not enabled. *CFMT*, 349 F.3d at 1340 ("Improvement and selection inventions . . . do not alone cast doubt on the enablement of the original invention."); *Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) ("There is no inconsistency in awarding a generic [claim] to one inventor, while awarding a patentably distinct species [claim] to another . . . .").

means to achieve, *see Amgen Inc. v. Sanofi, Aventisub LLC*, 987 F.3d 1080, 1087-88 (Fed. Cir. 2021) (insufficient identification of structure to perform claimed antibody function); *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365-66 (Fed. Cir. 1997) (insufficient support for claim to method of producing hormone where reaction materials and conditions not provided); *LizardTech, Inc. v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345 (Fed. Cir. 2005) (insufficient support for how claimed "processes" achieve "seamless DWT" result); *Trustees of Boston Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364-65 (Fed. Cir. 2018) (insufficient support for how "monocrystalline growth layer" can be "grown on" amorphous "buffer layer");[41] *MagSil Corp. v. Hitachi Global Storage Techs., Inc.*, 687 F.3d 1377, 1381 (Fed. Cir. 2012) (insufficient identification of devices that "caus[e] a change in the resistance by at least 10%"); or treatment methods for which there was inadequate data to support the claimed use. *See In re '318 Patent Infringement Litig.*, 583 F.3d 1317, 1327 (Fed. Cir. 2009) (insufficient data for claim to treating Alzheimer's with galanthamine).[42]

None of Mylan's cases involves a claim to a chemical compound or hydrate thereof defined structurally, which courts repeatedly have found enabled. *GSK I*, 2013 WL 4082232, at *8-13; *Endo*, 2014 WL 334178, at *30-33; *supra* II.A;[43] *see GSK II*, 744 F.3d at 731 ("The claims in this case, not involving functional claim language, do not present the fundamental

[41] In an attempt to analogize to *BU*, Mylan argues that "Merck fought—and won—a broad construction that encompasses *any hydrate*." Br. 20. But Merck never sought a construction of "a hydrate thereof" in claim 1. Rather, the defendants sought (and lost) a construction of claims 2, 3, and 21 that would have *excluded* "a hydrate." Dkt. No. 91 at 6; Dkt. No. 93-20 at 7-12.

[42] Mylan cites *Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1345 (Fed. Cir. 2021), which involved a claimed method of treating multiple sclerosis that the court found lacking in written description support because the specification failed to disclose adequate data.

[43] In reply, Mylan may cite *Plant Genetics Sys., N.V. v. DeKalb Genetics Corp.*, 315 F.3d 1335 (Fed. Cir. 2003), but like Mylan's other cases, the claims recited *functional* results (*e.g.*, "stably" transformed monocot plant cells) without showing how to achieve them. *Id.* at 1340.

difficulty presented by the claims in virtually all of the precedents on which Defendants rely.").

C. The asserted claims are enabled under the correct *Wands* analysis.

As reflected above, the '708 patent is enabled, which the *Wands* factors confirm:

Breadth of the claims, nature of the invention. The asserted claims cover and are coextensive with a single chemical compound—1:1 sitagliptin DHP—making their breadth "narrow." Tr. 913:2-9, 923:2-21, 925:18-926:5 (Myerson). Mylan disagrees, emphasizing that the claims cover "any physical form," Br. 20-21, but that is simply because all of them contain the compound that Merck invented and depicted in claim 1, Tr. 350:25-351:6 (Buckton), 913:22-914:21 (Myerson). The recitation "or a hydrate thereof" in claim 1 does not alter the breadth of the claims because "a hydrate" of 1:1 sitagliptin DHP is encompassed by the structure of the salt itself. Tr. 349:13-350:2 (Buckton); *see also GSK I*, 2013 WL 4082232, at *5 ("[T]he drug compound is the key structural feature[.]"); *Chern*, 2011 WL 5080233, at *3. Even if Mylan's framing were accepted, the term "hydrate" is narrower than "solvate," Tr. 353:20-355:6 (Buckton), the recitation of "solvates . . . does not render the claims unusually broad," and Merck has enabled the only hydrate known to exist. *GSK I*, 2013 WL 4082232, at *10; *supra* II.A.

Amount of guidance, working examples, quantity of experimentation. The '708 patent provides substantial guidance and working examples, which would have enabled the synthesis of every known form of 1:1 sitagliptin DHP. *Supra* II.A. That is more guidance than was provided in *GSK I* or any other case to consider enablement of solvates or hydrates. *Id.*

State of the prior art, relative skill, predictability. The study of crystal forms, including hydrates, is not new, and methods for discovering and characterizing them were well-known. Tr. 911:8-913:1, 926:6-928:2 (Myerson); DTX-43_20-40, _61-97; DTX-5_4. Dr. Buckton himself has studied hydrates "extensively," has "regularly ma[d]e and test[ed] hydrates," "discover[ed] hydrates as a property of doing screens," and "test[ed] and characterize[d]" them. Tr. 268:23-

269:4 (Buckton). The POSA could also generate amorphous forms by destroying crystal structures through known techniques. Tr. 920:20-23 (Myerson), 360:5-16 (Buckton), 722:5-14 (Vydra). It is also undisputed that phosphate salts "have a tendency to form hydrates." DTX-21_137; Tr. 355:22-356:5 (Buckton), 882:7-21, 916:4-10 (Myerson).

Mylan emphasizes that the discovery of polymorphs is unpredictable. Br. 21, 23. But that does not mean that compounds with polymorphic behavior lack enablement—to the contrary. *See GSK I*, 2013 WL 4082232, at *12-13; *Cai*, 2011 WL 6127936, at *6-10; *Germeyer*, 2010 WL 4961695, at *3. Mylan cites Dr. Myerson's opinions from the IPR, Br. 21, 23, but those opinions concerned the *obviousness* of claim 4 and did not rely on the '708 patent's teachings. For enablement, the POSA *does* have access to those teachings, and the '708 patent would have allowed the POSA to make every known form of 1:1 sitagliptin DHP. *Supra* II.A.

III. MYLAN'S WRITTEN DESCRIPTION DEFENSE FAILS

As with enablement, Mylan's written description challenge is divorced from the governing legal standard and rests on the mistaken notion that Merck was required to describe unknown, undiscovered hydrates. Br. 24-25. But "[a]n applicant is not required to describe in the specification every conceivable and possible future embodiment." *Cordis Corp. v. Medtronic AVE, Inc.,* 339 F.3d 1352, 1365 (Fed. Cir. 2003). To the extent Mylan asserts that Merck had to exemplify another hydrate to satisfy written description, the law is again to the contrary. *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1353 (Fed. Cir. 2011) ("[W]ritten description . . . does not demand either examples or an actual reduction to practice.").

The applicable standard—which Mylan never cites—is whether the patent describes a "representative number of species" or "structural features common to the members of the genus so that one of skill in the art can 'visualize or recognize'" them. *Ariad*, 598 F.3d at 1350. Mylan cannot dispute that *Ariad* is satisfied. As to representative species, the patent describes multiple

forms of 1:1 sitagliptin DHP—anhydrous and hydrate—and ways of synthesizing them. *Supra* II.A. As to common structural features, claims 1-3 define the claimed salts by their formal names and molecular structures, set forth verbatim in the specification. JTX-1, 2:44-3:45, 15:60-16:47; Tr. 349:3-351:6 (Buckton), 913:2-21 (Myerson). The POSA undisputedly would be able to "visualize or recognize" these structures, which are common to all forms of 1:1 sitagliptin DHP. Tr. 351:7-353:16 (Buckton), 913:22-915:11 (Myerson). On highly analogous facts, the Federal Circuit has found claims to have written description support. *GSK II*, 744 F.3d at 730; *see also Endo*, 2014 WL 334178, at *30-33.

Mylan attempts to distinguish *GSK II* on the basis that the compound in that case was "prone to solvate formation," Br. 24-25, ignoring that the same is true here; the claims are directed to a dihydrogen*phosphate* salt and Dr. Buckton conceded that phosphates have a "tendency to form hydrates." Tr. 355:22-356:5 (Buckton); *see* Tr. 882:7-21, 916:4-10 (Myerson); DTX-21_137; *supra* I.A.4. And the claims here—directed at "a hydrate" instead of all "solvates"—are narrower than in *GSK II*. Tr. 353:20-355:6 (Buckton).

Mylan cites language from *GSK II* in which the Federal Circuit expressed discomfort with patents that "preempt the future before it has arrived." Br. 25. But Mylan ignores that the Court found such a concern *not* applicable to the broader "solvate" claims in that case. As was true in *GSK II*: "The claims in this case, not involving functional claim language, do not present the fundamental difficulty presented by the claims in virtually all of the precedents on which [Mylan] rel[ies]." 744 F.3d at 731. "[Hydrates] of [1:1 sitagliptin DHP] are not distinguished by a particular performance property. The claim term does not assert coverage of yet-unidentified ways of achieving a desired result; it does not 'attempt to preempt the future before it has arrived.'" *Id.* Mylan's written description challenge is meritless and should be rejected.

Dated: February 25, 2022

Respectfully submitted,

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IN THE UNITED STATES DISTRICT COURT FOR THE NORTHERN DISTRICT OF WEST VIRGINIA

MERCK SHARP & DOHME CORP.

Plaintiff,

v. C.A. No. 1:19-cv-00101 (IMK)

MYLAN PHARMACEUTICALS INC., and **MYLAN INC.**

Defendants.

CERTIFICATE OF SERVICE

I certify that on this 25th day of February 2022, I electronically filed the foregoing "Merck's Brief in Response to Mylan's Opening Post-Trial Brief," with the Clerk of the Court using the CM/ECF system, which will send notice of the same to all counsel of record.

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